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Review Articles

The Adaptive Aerosol Delivery (AAD) Technology: Past, Present, and Future

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Abstract

Conventional aerosol delivery systems and the availability of new technologies have led to the development of "intelligent" nebulizers such as the I-neb Adaptive Aerosol Delivery (AAD) System. Based on the AAD technology, the I-neb AAD System has been designed to continuously adapt to changes in the patient's breathing pattern, and to pulse aerosol only during the inspiratory part of the breathing cycle. This eliminates waste of aerosol during exhalation, and creates a foundation for precise aerosol (dose) delivery. To facilitate the delivery of precise metered doses of aerosol to the patient, a unique metering chamber design has been developed. Through the vibrating mesh technology, the metering chamber design, and the AAD Disc function, the aerosol output rate and metered (delivered) dose can be tailored to the demands of the specific drug to be delivered. In the I-neb AAD System, aerosol delivery is guided through two algorithms, one for the Tidal Breathing Mode (TBM), and one for slow and deep inhalations, the Target Inhalation Mode (TIM). The aim of TIM is to reduce the treatment time by increasing the total inhalation time per minute, and to increase lung deposition by reducing impaction in the upper airways through slow and deep inhalations. A key feature of the AAD technology is the patient feedback mechanisms that are provided to guide the patient on delivery performance. These feedback signals, which include visual, audible, and tactile forms, are configured in a feedback cascade that leads to a high level of compliance with the use of the I-neb AAD System. The I-neb Insight and the Patient Logging System facilitate a further degree of sophistication to the feedback mechanisms, by providing information on long term adherence and compliance data. These can be assessed by patients and clinicians via a Web-based delivery of information in the form of customized graphical analyses.

Key words: Adaptive Aerosol Delivery technology, Adaptive Aerosol Delivery System, AAD, I-neb AAD System, I-neb Insight, patient logging system

Introduction

The conventional jet nebulizer powered by a compressor has been used for almost a century for delivery of inhaled drugs for the treatment of various respiratory disorders.[1] The nebulizer has become a well-established alternative to pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs), as it is ideal for delivery of high doses of drug, of drug mixtures, and of new drugs not formulated for pMDIs or DPIs.[2] The drawback with conventional jet nebulizers has been the waste of drug mainly during exhalation, the large variability in the delivered dose depending on the patient's breathing patterns, and the large residual with only 10 to 20% of the nebulizer fill volume delivered as aerosol to the patient. Recognition of the possibilities to improve nebulized drug delivery by addressing some of these shortcomings led to the development of "intelligent" jet nebulizers based on Adaptive Aerosol Delivery (AAD) technology.[3] The introduction of nebulizers based on the Vibrating Mesh Technology (VMT) has improved the efficiency of the aerosol delivery due to a smaller residual. These nebulizers do, however, still waste drug during exhalation due to continuous drug delivery without any adaptation to the patient's breathing patterns.[4] The latest iteration of the AAD technology, the I-neb AAD System, combines the mesh technology with the AAD technology.[5]

The AAD technology was first embodied in the HaloLite AAD System, which was codeveloped with Astra, Lund, Sweden, and made commercially available in 1997.[3] The basic nebulizer technology in the HaloLite AAD System was

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based on the Ventstream active venturi jet nebulizer technology. The AAD algorithm predicted the length of the patient's next inhalation based on the duration of the three previous inhalations, and delivered a pulse of aerosol into the first 50% of that inhalation. The HaloLite AAD System consisted of a battery-powered handpiece, including a mouthpiece, a medication chamber, an electronic control unit, and a compressor operated from mains electricity. The HaloLite AAD System was preset to deliver only 0.25 mL per preset dosage, and therefore, depending on the volume of drug in the vial used, a significant amount of drug remained as residual.

The Prodose AAD System was the second-generation AAD System, and was developed in conjunction with Schering AG (Bayer Schering Pharma AG, Berlin, Germany) for delivery of iloprost for treatment of pulmonary arterial hypertension, and launched in 2002.[3] Although based on the same aerosol generation technology, it offered significant improvements in convenience and flexibility over the HaloLite AAD System. The Prodose AAD System consisted of a compressor connected to a self-powered handpiece fitted with a liquid crystal display. Improved versions of the AAD algorithms designed for the HaloLite AAD System were used, which allowed the pulse of aerosol to be extended beyond 50% in cases when the patient's inhalation exceeded 2 sec. The main difference between the HaloLite and the Prodose AAD Systems was that instead of using a factory-programmed preset dose handset, the Prodose AAD System was designed with the AAD Disc to control drug delivery and the AAD Disc could be supplied with the drug.

The I-neb AAD System is the third-generation AAD System, and is substantially smaller and lighter than the previous AAD System nebulizers (Table 1).[5] The main parts of the I-neb AAD System (Fig. 1) are the body, the medication chamber assembly including the metering chamber, the mesh, and the mouthpiece. Due to the mesh design the I-neb AAD System is virtually silent.[5] Built into the body are the microprocessor that runs the AAD algorithm, the electronic aerosol generation circuit, the piezo element connected to the horn, the pressure sensor, the LCD screen, the radio frequency antenna for the AAD Disc, the patient logging system (PLS), the infrared transmitter/receiver for I-neb Insight, the battery, buzzer, and the vibration device for the tactile feedback. The I-neb AAD System is approved as a general purpose nebulizer in the European Union, and for the delivery of drugs that are approved for use with the I-neb AAD System in the United States.[5] For the purpose of this review of the AAD technology, the focus will be on the I-neb AAD System.

The AAD Algorithms

The I-neb AAD System can be operated in two breathing modes, the Tidal Breathing Mode (TBM; Fig. 2) and the Target Inhalation Mode (TIM; Fig. 2).[5] The breathing mode is selected by using a specific mouthpiece, which can be detected by the electronics in the I-neb AAD System (Fig. 1). In TBM, the patient breathes tidally though the mouthpiece, and this mode of inhalation is suitable for all patients who can use a mouthpiece. The results of a clinical study in which 52 patients with CF (age range 2–17 years) were transferred from jet nebulizers to the I-neb AAD System, indicate that patients as young as 2 years of age can use the mouthpiece.[6] In TIM, the patient is guided through feedback to make a slow and deep inhalation, which is suitable for patients who can use a mouthpiece and comply with the demands of that breathing maneuver.

TBM

The aim of the AAD algorithm in TBM is to continuously predict the length of the patient's next inhalation. Based on this information a pulse of aerosol can be delivered at the beginning of the next inhalation and end after 50% of the predicted inhalation time has expired. The average length of the past three inhalations is used by the AAD algorithm for the prediction of the length of the next inhalation. This means that the I-neb AAD System will only deliver aerosol starting on the fourth breath of each new treatment. Thereafter, the average inhalation time is updated after each subsequent inhalation. The pulse time is continuously monitored and adjusted by the algorithm depending on variations in the patient's breathing pattern. In cases when the patient's inhalation exceeds 2 sec, the pulse time is extended beyond 50% of the predicted inhalation time and up to ~1 sec before the start of the predicted exhalation.

A combination of a pressure sensor and a flexible valve in the I-neb AAD System is used to monitor the patient's inspiratory flow pattern (Fig. 1). The valve has a known pressure to flow characteristic, which allows the pressure measurement to be transferred, via an analogue-to-digital converter, to the processor running the AAD software and interpreted as a flow measurement. A waveform analysis program is used to ensure that the I-neb AAD System can operate effectively with breathing patterns typical for children from ~2 years of age to adults.[7] This ensures that the AAD algorithm remains sensitive for children without generating false triggers in adults. The waveform is monitored every 30 msec through the AAD software, which determines the slope of the curve over three consecutive 30 msec measurements (Fig. 2). A "positive" flow curve—two consecutive increases of at least 0.65 L/min—indicates that an inhalation is about to start. When the inspiratory flow rate is greater than 1.5 L/min the pulse of aerosol is triggered. Once an inhalation has started, the waveform is continuously monitored by the AAD software, to detect a "negative" slope—

Table 1. A Table Comparing the Different Features of the HaloLite, Prodose, and I-neb AAD Systems

	Year of launch	*Size (cm; h×w×d)*	*Weight (g)*	*Power (W)*	*Voltage (V)*	*AAD TBM*	*PLS*	*AAD Disc*	*AAD TIM*
HaloLite	1997	14×29×18	2700	200	240 AC	✓	✓		
Prodose	2002	18×14×29	3190	200	240 AC	✓	✓	✓	
I-neb	2004	15×6.5×4.5	210	6	3.8 DC	✓	✓	✓	✓

AAD, Adaptive Aerosol Delivery; PLS, patient logging system; TBM, Tidal Breathing Mode; TIM, Target Inhalation Mode.

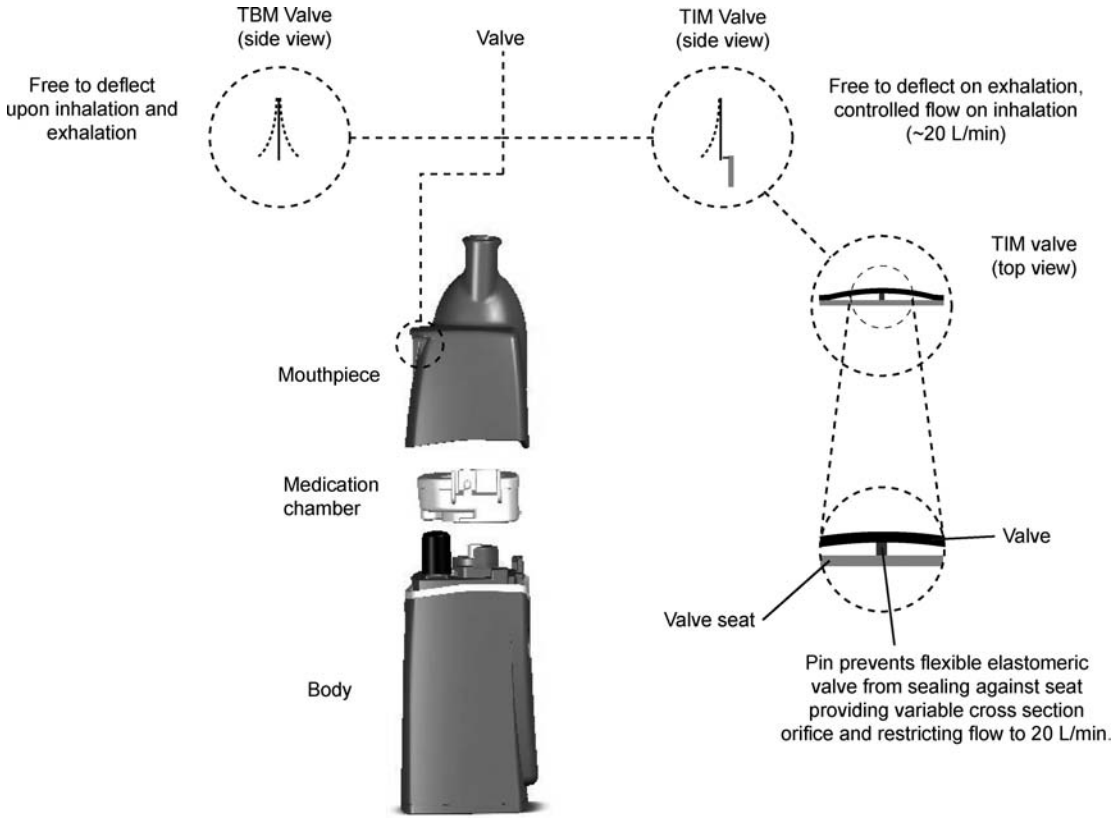

FIG. 1. The I-neb Adaptive Aerosol Delivery (AAD) System. The main components of the device are the mouthpiece, the medication chamber assembly, and the body. The I-neb AAD System has been designed to deliver aerosol with two different breathing pattern algorithms, the Tidal Breathing Mode (TBM) and the Target Inhalation Mode (TIM). In TIM the inspiratory flow through the valve in the mouthpiece is limited to ~20 L/min.

two consecutive decreases of at least 0.65 L/min—which would indicate the start of an exhalation. Once the flow reaches zero, the AAD software identifies this point as the end of inhalation. The analysis performed by the AAD software facilitates both an accurate triggering of the aerosol pulse, and the measurement of the inhalation time, which is used in a calculation of the moving average over three breaths to predict the next aerosol pulse time.

Table 2. A Summary Table of the Level of Compliance with the Correct Use of AAD System Nebulizers Documented in Clinical Studies

AAD System	*Number of patients*	*Age range (years)*	*Compliance level (%)*	*Reference*
AAD System prototype	125	<1–6	90%	14
HaloLite AAD System	121	<1–65	98%	15
HaloLite ped AAD System	47	<1–3	81%	16
HaloLite AAD System	50	7–53	84%	17
Prodose AAD System	19	11–45	90%	18
I-neb AAD System	96	[a]	96%	19
I-neb AAD System	70	53–80	95%	12
I-neb AAD System	42	12–57	97%	11

[a]Information not available.

TIM

The main aim of the long and slow inhalation is to reduce nebulization time in comparison with the TBM breathing pattern as a result of the increase in the total inhalation time per minute of treatment.[5] An improvement in lung deposition by reducing impaction in the upper airways is also achieved.[8] The aim of the AAD algorithm in TIM is to provide the patient with an optimal target time for each slow and deep inhalation. The AAD algorithm is used in conjunction with a mouthpiece designed with a special inhalation valve to restrict the inspiratory flow to ~20 L/min (Fig. 1). The initial target inhalation time for the slow and deep inhalation is set at 3 sec, which is equivalent to an inhaled volume of ~0.75 L. When the target inhalation time is reached, a vibrator informs the patient to end the inhalation. For the duration of the initial 3 sec of inhalation, aerosol is delivered during the first 2 sec followed by inhalation of room air without aerosol during the remaining 1 sec. This is to ensure that the aerosol is inhaled deep into the lung and remains there long enough to be deposited and not exhaled.[8] The AAD algorithm monitors the time "ΔT" between the vibrator signal and the moment when the patient stops inhaling (Fig. 2). During breathing, the inspiratory and

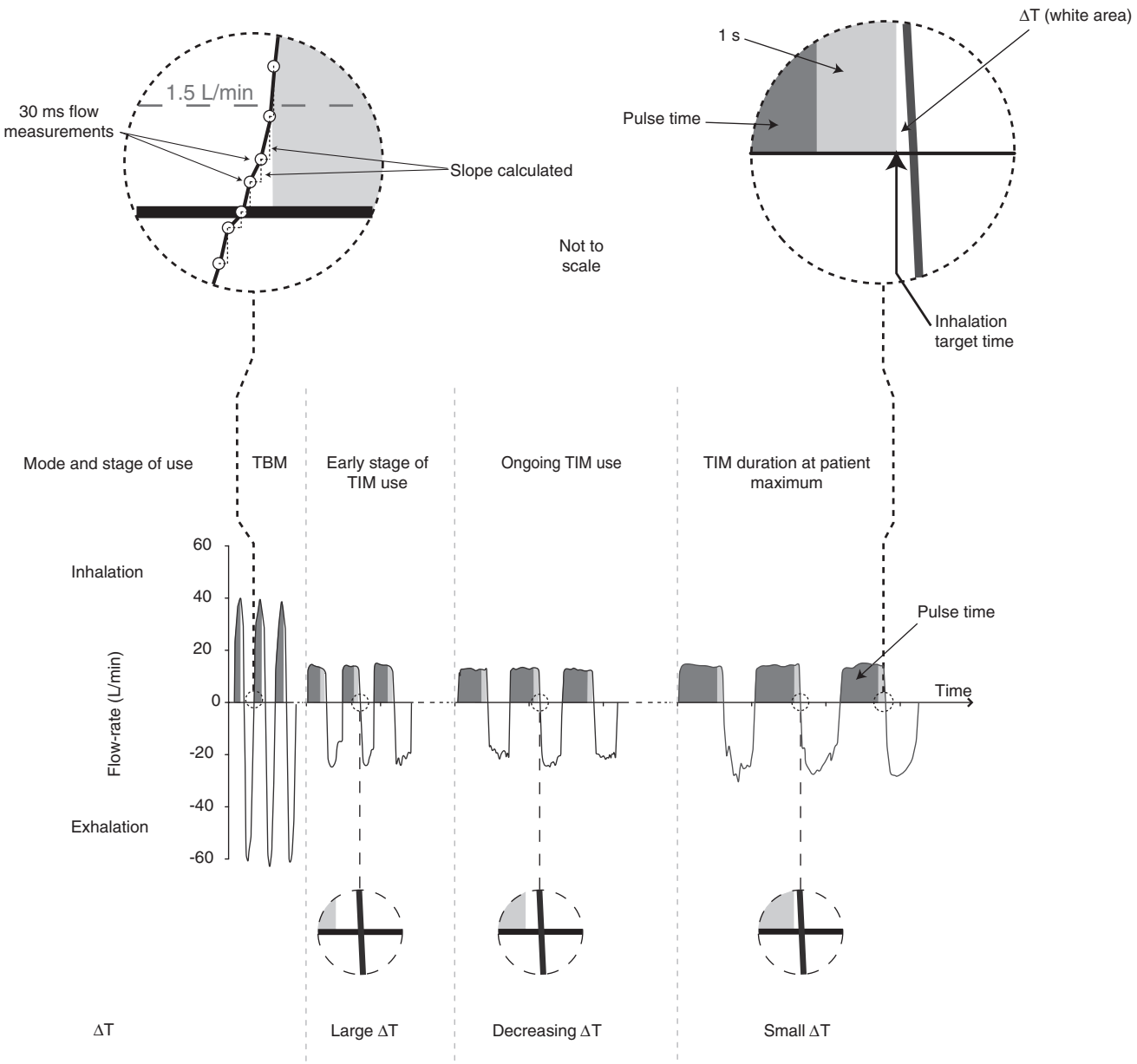

FIG. 2. Graphical presentation of the two breathing patterns used with the I-neb Adaptive Aerosol Delivery (AAD) System. The first part of the graph shows the patient's tidal breathing when using the I-neb AAD System in Tidal Breathing Mode (TBM). The second, third, and last parts of the graph show the process to extend the patient's slow and deep inhalations from a 3-sec inhalation (1-sec aerosol pulse) to an 8-sec inhalation (7-sec aerosol pulse) when using the I-neb AAD System in Target Inhalation Mode (TIM). The magnified area above to the left shows how the waveform is monitored every 30 msec through the AAD software, which determines the slope of the curve over three consecutive 30-msec measurements. Two consecutive increases of at least 0.65 L/min indicate that an inhalation is about to start, and when the inspiratory flow rate >1.5 L/min the pulse of aerosol is triggered. The magnified area above to the right shows the end of the inhalation during TIM. The ΔT time provides a measurement of when the patient has reached his or her instantaneous residual lung capacity, and allows the AAD algorithm to increase or decrease the length of the target inhalation time.

expiratory maneuvers are driven by different muscle groups. The inspiratory muscles are working against the flow restriction of the mouthpiece and if the lung is only partially inflated, it takes longer for the muscles to relax so that exhalation can start than it would if the lung was initially fully inflated.[9] Thus, the change from inhalation to exhalation is slower for a partially inflated lung than for a fully inflated lung. The ΔT time provides a measurement of when the patient has reached the instantaneous residual lung capacity, and allows the AAD algorithm to increase or decrease the length of the target inhalation time. The aim is to optimize the length of the target inhalation time to approximately 80% of the patient's forced vital capacity (FVC). Once the optimal target inhalation time has been set, the algorithm will adjust it to meet the patient's effort on each inhalation. At the end of the treatment, the achieved length of the target inhalation

time is filed in the memory for subsequent treatments. However, as the initial target inhalation time of 3 sec requires an inhaled volume of ~0.75 L, the patient should have an FVC ≥1.75 L to manage the slow and deep inhalation maneuver.[10] These requirements might make the use of the I-neb AAD System in TIM challenging for children, and for patients with poor lung capacity as these will not generate a significant ΔT.

Clinical experience with TBM and TIM

The I-neb AAD System is presently used in the treatment of patients with cystic fibrosis (CF), and pulmonary arterial hypertension.[5] A number of clinical studies have been performed to evaluate the I-neb AAD System in terms of patient acceptability and lung deposition.

The acceptability of the TIM breathing maneuver has been evaluated in 20 patients with CF during up to eight simulated nebulizer treatments with 10 min pauses between the treatments.[10] The study design involved lengthening of the patient's inhalation time over successive breaths with guidance from auditory and tactile (vibratory) feedback from the prototype I-neb AAD System. At the end of the first treatment, most patients felt that the instructions were easy to understand (90%) and that the vibratory feedback was pleasant (65%). Half of the patients found the procedure to be comfortable. At the end of the final treatment, most patients felt that the breathing maneuver was easy to understand (90%) and use (80%), but that the duration of the breath was too long (100%). Logged data revealed that 90% of patients were able to comply with the breathing maneuver. The two patients unable to comply had a forced vital capacity of <1.75 L. The average treatment time decreased from 288.4 to 141.6 sec during the first and final treatments, respectively. This study provided preliminary evidence of the acceptability of the TIM breathing maneuver in patients with CF and their ability to perform repeated TIM maneuvers during simulated nebulizer therapy with the I-neb AAD System.

A 3-month patient handling study of the I-neb AAD System in 42 patients with CF aged 12–57 years has been performed with the aim to evaluate compliance with the correct use of the I-neb AAD System, and treatment times.[11] The secondary variables included ease of use with the I-neb AAD System based on a questionnaire at the end of the study. The I-neb AAD System was supplied in both TBM and in TIM, and the patients were trained to use the TIM maneuver for the delivery of all their inhaled medications. If they were not comfortable with the TIM maneuver they could change to the TBM maneuver. There were a total of 10,240 complete treatments and of these 88% were in TIM. Compliance with the correct use of the I-neb AAD System was 97.6%. The mean treatment time for complete treatments in TIM was 4.20 min, compared with 6.83 min when using the I-neb AAD System in TBM. The responses to the questionnaires indicated that over 77% of the patients found the I-neb AAD System in TIM to be either: very easy, easy, or acceptable to use.

The I-neb AAD System in TBM has been compared with the patients' previous nebulizers in a multicenter study with 98 patients with chronic obstructive pulmonary disease aged 53 to 80 years.[12] The primary variables were ease of use and satisfaction assessed after 3 months of use of the I-neb AAD System (assessed at visit 2) and after 3 months of use of the patient's previous nebulizer system (assessed at visit 1) using matched questions from pre- and poststudy questionnaires. Quality of life was also assessed at visits 1 and 2 using a validated Chronic Respiratory Questionnaire (CRQ), which consists of dyspnea, emotional function, fatigue, and mastery domains. Patient responses on the ease of use and satisfaction questions significantly ($p \leq 0.001$) favored the I-neb AAD System compared with the patient's previous nebulizer system. In addition, significant ($p \leq 0.015$) improvements in the CRQ dimensions of dyspnea and fatigue were reported with the I-neb AAD System compared with the patients' previous nebulizer systems.

The lung deposition of a radiolabeled aerosol from the I-neb AAD System with TBM and TIM breathing patterns was evaluated in a randomized, open-label, crossover study of 12 healthy subjects.[8] The results showed that the mean lung deposition was significantly higher when using the I-neb AAD System in TIM (73.3%) than in TBM (62.8%). The mean exhaled fractions were low (<1%) for both breathing patterns. The nebulization time was significantly shorter in TIM (3.0 min) than in TBM (4.7 min). With the combination of a high lung deposition, almost no loss of aerosol during exhalation, and a short nebulization time the I-neb AAD System with the TIM breathing pattern should be of special value to patients who require multiple daily dosing of aerosolized medication, are using drugs that should not be wasted into the room air, or would benefit from a more efficient delivery system.

Aerosol Generation and the VMT

The I-neb AAD System has been designed with a specific VMT to generate an aerosol. The VMT consists of an ultrasonic horn driven by a piezo element and a platinum mesh with ~7000 holes with an average diameter of 2 μm (Fig. 3). The liquid (solution or suspension) fills the gap between the horn and the mesh by gravity, and is pumped through the mesh by the vibrations of the horn (178 kHz; Fig. 1). When the liquid in the medication chamber has been delivered, an electronic control circuit detects the change in power required by the horn, signaling the end of nebulization. The piezo element connected to the horn has a variable power range for the optimization of the aerosol output rate, which allows the performance of the aerosol generator to be tailored to the specific drug formulation.

The mass median aerodynamic diameter (MMAD) of the aerosol pumped through the mesh has been determined using an albuterol solution and the Next Generation Impactor (NGI; MSP Corporation, St. Paul, MN, USA). The I-neb AAD System was configured with a 0.25 mL metering chamber and programmed to operate in a continuous mode to facilitate continuous aerosol production at power level 10. The MMAD of the albuterol solution was 3.9 μm, the geometric standard deviation 1.7, and the fine particle fraction 67%.[13]

The piezo element used in conventional ultrasonic nebulizers has made these nebulizers less suitable for use with drug suspensions and drugs that are heat sensitive. The piezo element driving the ultrasonic horn in the I-neb AAD System operates at ~10% of the power of the piezo element

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